

Contemporary Insights into Cancer Cachexia for Oncology Nurses

Deborah A. Boyle

Advanced Oncology Nursing Resources, Phoenix, Arizona, USA

Corresponding Author: Deborah A. Boyle, MSN, RN, AOCNS®, FAAN. Advanced Oncology Nursing Resources, Phoenix, Arizona, USA. E-mail: deboyle@cox.net

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ABSTRACT

Cachexia is a complex, multiorgan phenomenon targeting skeletal muscle resulting from systemic metabolic imbalances. Multifocal in nature, its ultimate outcome is significant muscle degradation and loss of adipose tissue exhibited as the “wasting syndrome” which is associated with significant functional decline. Currently, there are no approved biomarkers for screening nor therapeutic options to manage cancer cachexia. Furthermore, multiple psychosocial sequelae characterize the

patient and family coping paradigm. Heightened education about the pathophysiology of cancer cachexia and awareness of intra-familial emotional distress can enhance oncology nurses' advocacy about, and attentiveness to, this common manifestation of advanced cancer.

Key word: Cachexia, eating, food conflict, muscle wasting, weight loss

Introduction

A distinguishing feature of solid tumors is their propensity to metastasize. This extension of cancerous cells beyond the site of initial growth is the cause of death in the majority of patients who die from cancer.^[1-3] Cancer cachexia is a common corollary of advanced cancer due to its molecular linkage with the metastatic process.^[4] It is often overlooked and rarely controlled.^[5] Consider the following facts. Cachexia occurs in:

- More than 50% of patients with liver, pancreas, lung, head and neck, gastric, and colorectal primary tumors
- 50%–80% of patients with advanced cancer; and
- Greater than 80% of patients in their last weeks of life.^[6-10]

In addition, cachexia is responsible for 20% of deaths from cancer related to cardiac arrhythmias, hypoventilation, thromboembolic events, cardiorenal dysfunction, and/or a compromised immune system.^[11,12] Other negative

corollaries of cachexia include an association with reduced efficacy of antineoplastic therapies, enhanced treatment toxicity, heightened incidence of surgical complications, and decreased overall survival.^[11,13,14]

Pathogenesis

The term “Cachexia” has Greek origins, namely “Kakos” and “Hexis” meaning “Bad Condition.”^[15] This multiorgan syndrome is prompted by reduced food intake and metabolic dysregulation (i.e., elevated energy expenditure, excess catabolism, inflammation) that triggers skeletal muscle loss.^[16,17] Anorexia or the reduced desire for food (i.e., loss of appetite) results from the impaired central nervous system (CNS) triggering due to presence of tumor byproducts and/or immune responses to the tumor.^[9] Chemotherapy may also be an etiology due to CNS anorectic effects that evolve through neuronal dysregulation

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in the hypothalamus.^[18] Other causes of altered food intake may be present and contribute to anorexia particularly in patients with advanced disease [Table 1].

An oncologic paraneoplastic syndrome, cancer cachexia is a complex disorder marked by excessive catabolism which causes alterations in lipid, protein, and carbohydrate metabolism, systemic inflammation, and insulin resistance.^[6,18,19] Its manifestations include involuntary weight loss evidenced in skeletal muscle, adipose tissue, the heart, intestine, kidney, liver, and brain.^[5,10,11,20,21] The tumor is the principle prompt of metabolic reprogramming that leads to the objective presentation of the “wasting” phenomenon.^[16,18] Skeletal muscle and adipose tissue are the primary targets throughout cancer cachexia’s progression.^[18,22] While muscle atrophy is the most obvious manifestation of cachexia, multiple organ dysfunctions are co-occurring subclinically [Figure 1].

Skeletal muscle is one of the most metabolically active tissue lines and serves as a repository of protein and amino acids.^[20] Its contraction requires considerable energy to function optimally.^[10] Muscle mass loss evolves due to an imbalance between anabolic and catabolic processes.^[9] Of note is that human skeletal muscle represents 40% of body weight and that once muscle mass has been impaired from cachexia, it has limited capacity for regeneration. The combination of muscle degradation with atrophy and the concomitant loss of adipose tissue ultimately leads

to progressive overall functional decline.^[9,13,22] Elderly cancer patients may exhibit more profound cachexia due to reduced muscle mass associated with aging.^[23] The enhanced lipid breakdown in white adipose tissue may also cause a browning discoloration of the skin which usually is indicative of cachexia’s progression.^[22]

Cardiac Implications of Cancer Cachexia

While skeletal muscle mass and adipose tissue are primary targets of cachexia, other organs such as the heart may experience damage. It is estimated that 20%–30% of cancer patients die from cardiovascular causes.^[24] Of note, is evidence of symptom presentation in patients with advanced cancer correlating with heart failure (i.e., shortness of breath, pulmonary congestion, decreased mobility and performance status, sudden death).^[25] While historically these symptoms have been considered an end-product of disseminated cancer, they may in fact characterize a degenerative form of cardiomyopathy.

Numerous cellular wasting processes may impact the structure and functioning of cardiac conduction pathways ultimately resulting in heightened arrhythmia risk.^[26] In a sequential manner, cardiac atrophy leads to impaired cardiac contractility and reduced heart rate.^[18] In addition, cancer-induced metabolic alterations may affect insulin and glucose metabolism, and iron uptake which can also affect cardiac and skeletal muscle function.^[16] Impaired cardiac innervation and blood hyper-coagulability may also play a role in increased cancer-related mortality.^[18] Hence, the sudden death of a patient with advanced cancer may be precipitated by cardiac dysfunction resulting from the loss of skeletal muscle mass.^[27] Debilitation in respiratory muscle function may exacerbate cardiac compromise.^[4,16] Figure 2 depicts cancer-associated cardiac consequences with potential adverse corollaries.

As the field of cardio-oncology evolves, future approaches to cachexia management may include the evaluation of patient functional status and biomarker-driven evidence of cardiac muscle wasting to consider the prophylactic use of defibrillators.^[28] This in concert with the administration of potentially cardio-toxic antineoplastics (i.e., anthracycline agents) and irradiation to the left chest needs to be considered in risk evaluation.^[15,18,29] A contemporary increase in knowledge about cachexia’s manifestations in the heart’s functioning has led to the naming of a parallel entity called “Cardiac cachexia.”^[16]

Screening, Staging, and Assessment

Involuntary weight loss in a cancer patient is generally overlooked and rarely managed in an aggressive manner.

Table 1: Etiologies of altered food intake

Food aversions
Consistency
Smell
Taste
Appetite changes
Absence of appetite trigger
Early satiety
Functional difficulties
Dry mouth
Dysphagia
Esophagitis
Indigestion/heartburn
Mucositis
Bowel alterations
Bloating
Constipation
Diarrhea
Mood disturbances
Depression
Co-occurring symptoms
Drowsiness
Fatigue
Insomnia
Nausea
Pain
Shortness of breath

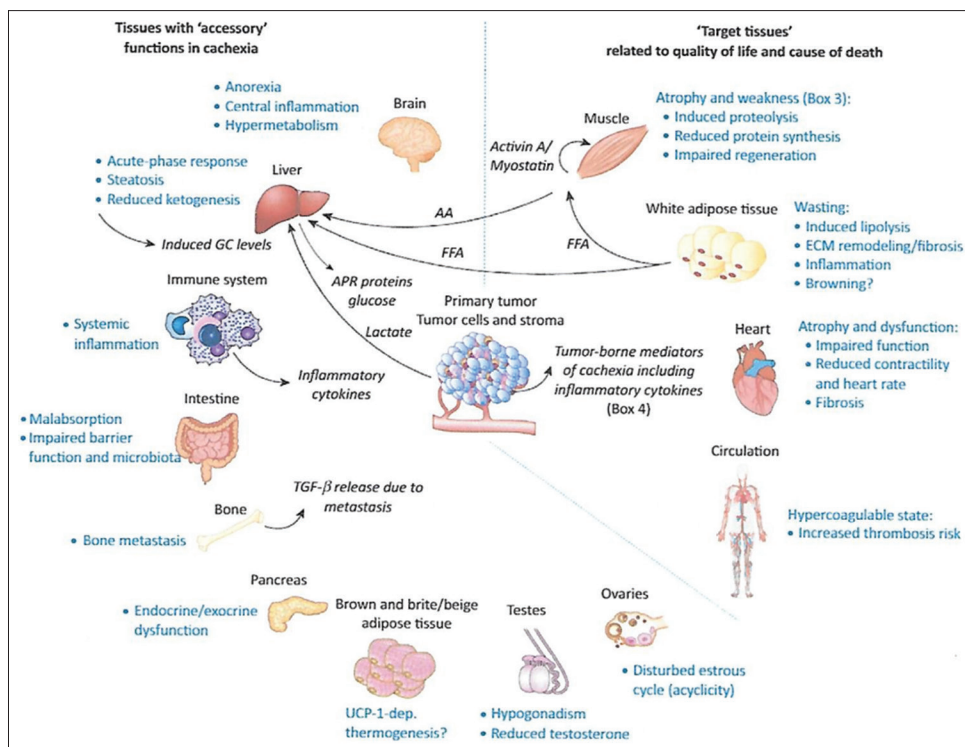


Figure 1: Systemic implications of cancer cachexia. Reprinted with permission^[18]

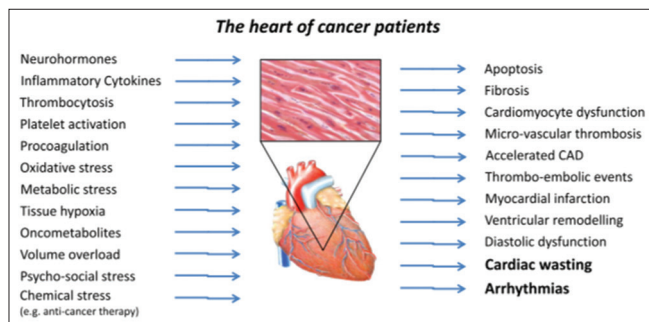


Figure 2: The heart of cancer patients. Reprinted with permission^[26]

Yet, it is a hallmark symptom of cachexia’s presence and often is a predictor of reduced survival. Once a patient experiences weight loss equal to or more than 5% of their usual weight, they already are at risk for increased mortality.^[30]

Screening

Computerized tomography (CT) or magnetic resonance imaging (MRI) is the first choice for analyzing body composition. CT or MRI of the lumbar spine (L3) are preferred as both skeletal muscle and adipose tissue in this region correspond to whole-body dimensions.^[5] Of note is that this landmark is present in routine abdominal CT scans precluding the need for additional radiologic evaluation.^[31] Ideal muscle depletion parameters include those identified at the L3 site and anthropometric mid-arm circumference [Table 2].^[18]

To date, there have been no approved clinical biomarkers for cancer cachexia. However, their future identification will be increasingly instrumental in cachexia’s early recognition. Potential biomarkers are classified as those originating from the host (i.e., cachexia-inducing factors, muscle, and fat wasting products), the tumor (i.e., tumor-necrosing factor), and both host and tumor (i.e., inflammatory cytokines, micro RNAs).^[14] Bruggeman *et al.*,^[31] noted that the combination of elevated C-reactive protein, weight loss, and nutritional intake, may be used in the future as a combined measure of cachexia. Other imminent biomarkers may include the presence of increased inflammatory cytokines (i.e., interleukin 6, tumor necrosis factor), urine levels of lipid mobilizing factor, and interleukins identified in tissue biopsy samples.

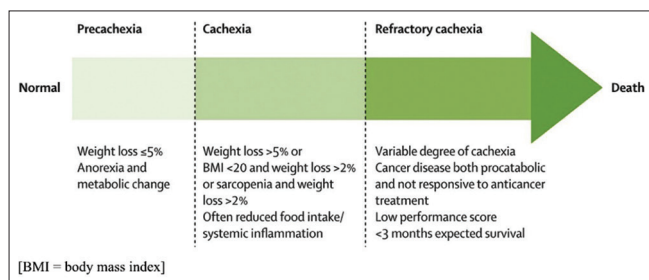
Staging

Cancer cachexia is conceptualized as a continuum, distinguished by three stages: Pre-cachexia, cachexia, and refractory cachexia.^[8,32-35] Figure 3 depicts characteristics of each stage. Of note, is that by the time cachexia is clinically recognized (i.e., stage 2), it usually is resistant to interventions; yet these patients have been the most studied to date.^[31,37]

Pre-cachectic patients will be the targeted focus of study in the future. Metabolic abnormalities precede weight loss during this phase and patients often maintain their usual functional status. Monitoring these

Table 2: Quantification of muscle depletion^[18]

Site	Men	Women
L3 (cm ² /m ²)	<55	<39
Mid-arm circumference (cm ²)	<32	<18

Figure 3: Stages of cancer cachexia^[36]

abnormalities (i.e., albumin, C-reactive protein, and novel approved biomarkers) prior to weight loss in tandem with early intervention will offer patients the best chance of a therapeutic response to future approved therapies. The presence of cachexia correlates with more pronounced physical changes, significantly decreased food intake, and often the need for assistance with daily activities.^[13,15,33] The presence of manifestations indicative of refractory cachexia often portend death within months.

Measurement instruments

In addition to laboratory findings, biomarkers, body mass index, and weight loss, subjective reports of quality of life, functional status, anxiety, depression, appetite, anorexia, family distress, and caregiver burden have also been reported as outcome measures. Instruments often used within the context of clinical trials include the 12-item Functional Assessment of Anorexia/Cachexia Treatment, and the EORTC health-related quality of life, cachexia symptom-focused QLQ-CAX 24.^[31,36] Future outcome indices may include patient and family satisfaction, functional status identified through pedometer reading, morphometrics, novel biomarkers, and muscle mass (not just body mass index) especially if exercise and nutrition interventions are integrated early into the treatment paradigm.

Therapeutic Approaches

Currently, there is no established standard of care to manage cancer cachexia nor an Food and Drug Administration (FDA)-approved drug to treat it.^[14,18] Numerous issues to date are associated with this unfortunate reality. They include targeting interventions that focus on patients with refractory cachexia who are not amenable to treatment.^[31] Small sample size and inconsistent use of outcomes measures are other problems.^[10] Furthermore, the historical management of cancer cachexia has used

a single-agent, “Magic Bullet” approach which does not address the multisystem pathways associated with this clinical syndrome^[9,11,12] Figure 4. identifies agents used to manage the sequelae of cachexia; specifically to improve appetite, regulate inflammatory responses, and mediate anabolic and catabolic processes. Contemporary investigational drugs based on their mechanism and site of action are highlighted in Figure 5.

The efficacy of other non-regulated interventions should be questioned. Artificial nutrition and hydration are not indicated in refractory cachexia.^[13] They not only do not improve survival but also are correlated with potential vomiting/regurgitation and aspiration.^[5] Currently, there also are no evidence-based results supporting the use of cannabis.^[15] However, in the future setting of randomized controlled trials with purposeful choice of cannabis extract (i.e., natural vs. synthetic derivative) and more rigorous dose scheduling, future research may reveal efficacy.^[38] Megestrol acetate (i.e., Megace) for appetite stimulation is the only FDA-approved for use in AIDS-associated cachexia.^[39] The absence of indications in other illnesses stem from research findings that weight gain appears to be related to an increase in body fat and fluid retention without gain in lean body mass.^[22] In addition, a concern about the use of Megace acetate in cancer patients also is associated with its red box warning about potential thromboembolic events.^[19]

Nearly all the clinical trials to date have focused on pharmacologic interventions and have not integrated behavioral or psychosocial therapies.^[22,40] Potential benefits of exercise include positive modulation in protein expression, improvement in aerobic capacity, and conservations of skeletal muscle mass with improved muscle function.^[12,18] A focus on nutrition therapy could potentially enhance the provision of energy fuels with protein-rich formulations to maximally support muscle mass and anabolism.^[41] Such therapies could interfere with the crescendo of catabolic stimuli such as muscle catabolic signaling. In the future, consideration of diet, exercise, adherence to nutritional therapies, and psychosocial counseling will most likely be researched within of a paradigm of multidisciplinary approach.^[31,42,43] A prototype for combined, multidisciplinary therapy is the Multimodal-Exercise, Nutrition and Anti-Inflammatory medication for Cachexia trial.^[44] In the meantime, the American Society of Clinical Oncology has published evidence-based guidelines for the current management of cancer cachexia which are outlined in Table 3.^[45]

Psychosocial Considerations

The pervasive emotive response of sustained helplessness generated by cancer cachexia has been termed the “Weight

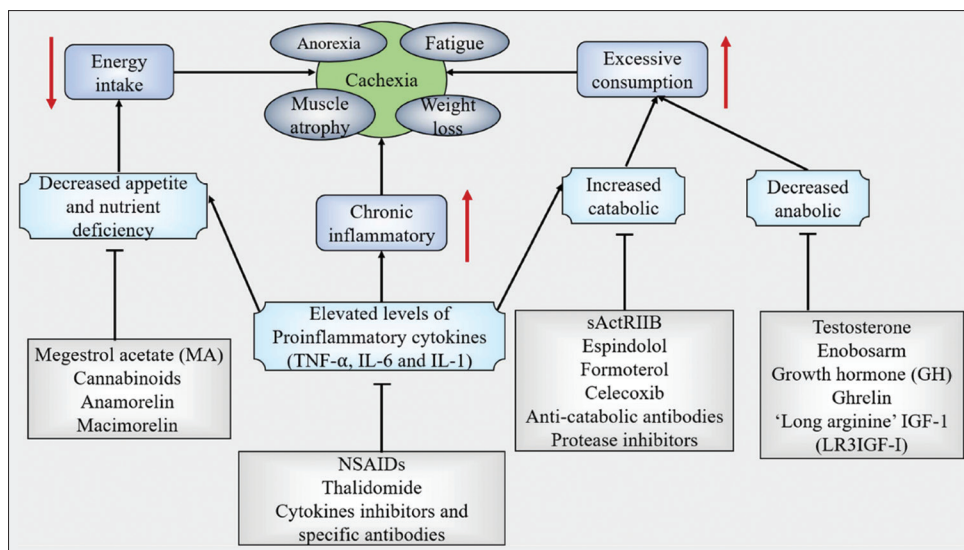


Figure 4: Targeted Pharmacological Management of Cancer Cachexia. Reprinted with permission^[9]

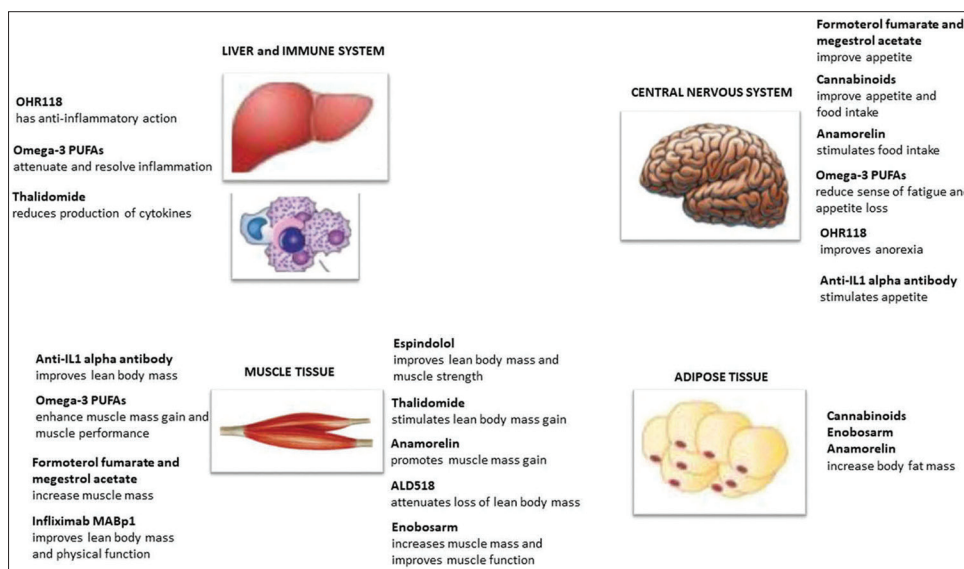


Figure 5: Investigational drugs for cancer cachexia tested in phase I and II clinical trials. Reprinted with permission^[21]

loss taboo” which is experienced by patients, their caregivers, and health care professionals.^[46] For patients, cachexia prompts distress emanating from alterations in self-image, self-esteem, and socialization norms.^[47] Even embarrassment over one’s appearance and debility may prevail.^[48] Refractory cachexia is a visible sign of cancer’s progression. It is a persistent reminder to patients and those around them that they are declining, not recovering. Cachexia makes the disease visible, indicating the proximity of disease progression and likely death.^[23] With functional decline also comes increased dependence on others, much feared consequence of life-threatening illness. Reliance on caregivers often encompasses meal preparation, assistance with basic needs, and transportation, all of which are associated with the perception of being a burden.^[49] Hence,

due to the magnitude of negative corollaries, minimizing negative corollaries, and the patient's focus on minimizing eating problems is common.

There is growing evidence that caregivers exhibit more distress than patients within the context of cancer cachexia.^[50] Much of this intra-familial discord focuses on the erroneous perception that increased eating will increase survival.^[5] Additionally, alterations in eating norms influence communication exchange within the family. Since eating and dining are common social events, changes in these patterns often leave loved ones feeling isolated and distraught. Family members often experience feelings of futility related to the energy they assert in food preparation and rejection while watching patient waste away.^[51] Family caregivers often view their primary role

as nourishing their family, thus when impediments to this responsibility evolve, they may experience a sense of failure, even shame.^[52] Cultural considerations about the role of food in illness also must be considered. In many Asian cultures, for example, food intake and enhancing feeding are perceived as mechanisms of showing hope, care, love, and respect.^[37,53,54] Within the context of cancer cachexia, Amano^[55] identified eight items that cause the most distress in family caregivers:

- I want attention to be paid to my distress about the patient's eating
- I feel that a lack of nutrition makes the patient's condition worse
- I wonder what kinds of food the patient can eat
- I wonder which nutrients the patient should preferentially consume
- I wonder how the patient can eat more
- I feel more medical support about the patient's daily diet is needed
- I feel that the patient disregards the effort that I show by making his/her meals
- I feel sad because the patient cannot enjoy dinner with me.

Conflict over food may become the norm and evolve into an issue of control, representative of a clash between the family caregiver taking charge and the patient struggling to maintain a sense of autonomy.^[51,55] For the patient, meals no longer bring pleasure but herald conflict, and at most, represent basic survival.^[47] Table 4 summarizes the varied elements of intra-familial food-related distress and supports the opinion that psychosocial interventions need to be a mainstay of family-centered care within this construct.

Finally, there are food-associated stressors associated with the patient and family's interaction with the cancer care team. In particular, family caregivers experience frustration about the team's lack of recognition of cachexia as a problem. The failure to discuss or question the presence and prominence of this syndrome leaves the family feeling

ill-equipped in knowing how to manage this problem.^[56] Dewey and Dean^[57] research identified that nurses offered suggestions for maximizing calorie and protein intake but only after the patient and/or family asked for assistance. The lack of a distinct management approach to cancer cachexia was indicative of a culture of avoidance which was especially troubling to caregivers.^[58]

Implications for Oncology Nurses

There are numerous ramifications for nursing within the realm of cancer cachexia. For patients with advanced disease at diagnosis, cancer cachexia may be present along the entire illness trajectory.^[46] Nurses working in sub-specialties of gastrointestinal, pulmonary, and radiation oncology need to have a sophisticated understanding of cachexia and screening guidelines in place. The Malnutrition Screening Tool is a validated, brief, user-friendly instrument to determine the risk for malnutrition in cancer care.^[59] Ideally this tool should be used sequentially with patients ultimately screening positive for risk being referred to registered dietitians. Built-in prompts in the electronic medical record can facilitate screening compliance.^[60]

An interdisciplinary team is ideally required to optimize the multifaceted management of this complex syndrome. In the absence of such, lobbying for consultation by these colleagues is indicated. Having the closest and continued proximity with patients also affords oncology nurses opportunities to identify research questions. Several issues that require study include interventions to optimize adherence to therapy recommendations, elucidating stage-specific distress themes of relevance, managing the sequelae of cachexia within patient/family dyads, and determining if the magnitude of weight loss is correlated with caregiver distress.^[34,40,48,55]

Conclusions

Nutrition is an important component of cancer care to many patients and family caregivers. Engaging in dietary

Table 3: Synopsis of major recommendations of the American Society of Clinical Oncology guidelines for Nutritional and Pharmacological Interventions in the Management of Cancer Cachexia^[45]

Intervention category	Recommendation
Nutritional	Clinicians may refer patients with advanced cancer and loss of appetite and/or body weight to a registered dietician for assessment and counseling, with the goals of providing patients and caregivers with practical and safe advice for feeding; education regarding high protein, high caloric, nutrient dense food; and advice against fad diets and other unproven or extreme diets Outside the context of a clinical trial, clinicians should not routinely offer enteral tube feedings or parenteral nutrition to manage cachexia in patients with advanced cancer
Pharmacologic	Evidence remains insufficient to strongly endorse any pharmacologic agent to improve cancer cachexia outcomes; there are currently no FDA-approved medications for the indication of cancer cachexia Clinicians may offer a short-term trial of a progesterone analog or a corticosteroid to patients experiencing loss of appetite and/or body weight
Other	Outside the context of a clinical trial, no recommendations can be made for other interventions such as exercise for the management of cancer cachexia

FDA: Food and drug administration

Table 4: Cachexia-associated elements of family caregiver distress^[8,22,46,48-51,53,56]

Social/relationship changes
Caregiver now eats alone
Regret not being in kitchen together and having social exchange at meals
Miss family gatherings and special events due to patient aversion of circumstances including food
Discomfort undressing in front of loved ones R/T body image changes
Family communication
Patient willingness or ability to eat diverges from family/caregiver expectations
Heightened sensitivity about initiating food-related topics in conversations
Patient misrepresents (i.e., overestimates) food intake to avoid conflict
Patient hides food to appear that intake is greater than reality which garners mistrust
Communication with healthcare professionals
Experience frustration when weight loss not acknowledged as a problem
Feelings of isolation in absence of professional information and support regarding symptom concerns
Perceived trust and partnership with professionals dissolved
Hypervigilance
Watchfulness/hovering behaviors over patient intake
Added time and energy in food selection and preparation to encourage intake
Monitoring weight changes
Emotional adversity
Rejection of food perceived as rejection of caregiver
Feelings of helplessness
New prominence of anger
Guilt/regret over efforts to promote eating upsets patient; initiating conversations that prompt arguments/feel responsible
Anxiety/worry/fear prominent reactions to continued downward cycle despite best efforts
Sadness: Mourn “the way things used to be;” anticipatory grief stemming from feeling “nothing works” and the end is near
R/T: Related to

interventions represents an enhanced sense of personal control in managing cancer. Yet, professionals’ lack of awareness of the importance of this component of patient care in tandem with minimal resourcing of clinical dietitians, often positions nutrition support as an unmet need.^[61]

Cachexia is not simply a nutritional aberrancy.^[4] Rather, it is a common, complex, and usually lethal multiorgan disorder with no effective therapies. Due to its poor prognosis and considerable influence on patient and caregiver distress, cancer cachexia is representative of the phenomenon of suffering.^[46] Nutrition is an important component of cancer care to many patients and family caregivers. Engaging in dietary interventions represents an enhanced sense of personal control in managing cancer. Yet, professionals’ lack of awareness of the importance of this component of patient care in tandem with minimal resourcing of clinical dietitians, often positions nutrition support as an unmet need.^[61] Nursing advocacy for the enhanced recognition and management of cancer cachexia requires more deliberative education about this syndrome.^[62] Increased knowledge can leverage

frontline oncology nurses to solicit interdisciplinary support to maximize symptom management. Greater professional education can also increase nurses’ awareness about cachexia and help transform a culture of avoidance to one of inclusion by discussing its prominence with patients and families.^[58]

This author has noted important corollaries between cancer-related fatigue and cancer cachexia. Historically, fatigue was perceived as a common symptom with no interventions available to address its prominence. Recently, however, this phenomenon has been the focus of considerable research to optimize its management. Similarly, as cachexia’s complex multifocal etiologies become increasingly understood, the possibility for effective management can be anticipated.

In today’s oncology nursing practice environment, the clinical presence of cachexia portends trepidation and often despair in patients and families. An oncology nurse dually skilled in the provision of physical and emotional comfort is needed to enhance living regardless of patient prognosis. Dame Cicely Saunders summed it best with her intuitive historic reflection.^[63]

I once asked a man who knew he was dying what he looked for most in the people caring for him. He paused for a moment and said, I look to see if they are trying to help me. Saunders then shared, You see, he did not ask for success, he asked only for the effort of trying.

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Conflicts of interest

There are no conflicts of interest.

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